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Differential Diagnosis of Osteogenic Tumors in the Context of Osteosarcoma

Mulazim Hussain Bukhari, Samina Qamar and Farwa Batool

Abstract

Primary bone tumors are rare, but osteosarcoma (OS) is the fourth commonest non-hematological primary neoplasm of the bone in the adolescence, and the other three commonest neoplasms, in descending order, are leukemia, brain tumors, and lymphoma. The commonest presenting complaints are swelling and aches. These tumors cannot be diagnosed without the help of radiology. There is a wide age range of these neoplasms commonly appearing in the second and third decade of life with a peak incidence in early teens. Males are affected more than females. The exact cause of osteosarcoma is unknown. However, a number of risk factors, like genetic predisposition, some existing bone diseases, environmental risk factors, and radiations, have been identified. If the bone tumors are viewed by clinical, radiological, and histopathological perspectives, the correct diagnosis can be made easily. Chemotherapy combined with surgery is the standard treatment modality with better 5-year survival rates. Elevated AKP is an important prognostic factor in this malignancy.

Keywords: aggressive osteoblastoma, osteogenic tumors, osteoma, osteoid osteoma, osteoblastoma, osteogenic sarcoma

1. Introduction

Primary neoplasm of the bones is relatively uncommon. Among these tumors, the osteosarcoma is the commonest primary malignant tumor, comprising of approximately 35% of all bone malignant tumors, followed by others like chondrosarcoma (25%), Ewing sarcoma (EWS) (16%), and chordomas (8%). This malignant tumor can arise from any bone, mainly usually in the metaphyseal (growth plates) long bones of the extremities, but the jaw, pelvis, and ribs may be the sites of origin [1].

The nomenclature of bone tumors are described in “the World Health Organization (WHO)” classification system [2]. We are adopting a table from this classification to review the pathological diagnostic criteria of these lesions. A number of variants of osteosarcoma exist, including conventional types (osteoblastic, chondroblastic, fibroblastic, telangiectatic, multifocal, parosteal, and periosteal) (**Table 1**) [3].

The histological pictures of bone tumors alone are not enough to make a differentiation between osteosarcoma and benign tumors or other malignancies of the bone; therefore, radiological and clinical help is needed to make the final diagnosis of osteogenic sarcoma. Therefore, the chapter will not only address osteosarcoma but will also discuss all osteogenic tumors stepwise [1].

Benign	Intermediate	Malignant
Osteoma	Osteoblastoma	Low-grade central osteosarcoma (OS)
Osteoid osteoma		Conventional OS Chondroblastic OS Fibroblastic OS Osteoblastic OS
		Telangiectatic OS
		Small cell OS
		Parosteal OS
		Periosteal OS
		High-grade surface OS
		Secondary OS

Table 1.
WHO-based classification of osteogenic tumors of the bone.

This chapter will mainly focus on general clinical, imaging, and histopathological characteristics, which will aid in diagnosis but may add a little to advances in tumor biology or treatment of the multitude of bone tumors described in this chapter.

The exact cause of osteosarcoma is unknown. However, a number of risk factors, like genetic predisposition, some existing (Paget disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses and retinoblastoma) bone diseases, environmental risk factors, and radiations, have been identified.

Keeping in mind the importance of this malignancy, it is therefore important to understand the other osteogenic tumors before reaching the importance of osteosarcoma; we will describe the differential diagnosis of osteogenic tumors in the context of osteosarcoma.

2. Osteoma

It is a benign neoplasm exclusively seen in flat bone of skull and face. Microscopically it consists of the mature lamellar bone. Multiple osteomas are associated with Gardner’s syndrome (colonic polyposis). Sometimes it involves other than the skull and face, as surface lesions of parosteal type (**Figure 1** and **Tables 1** and **2**) [4].

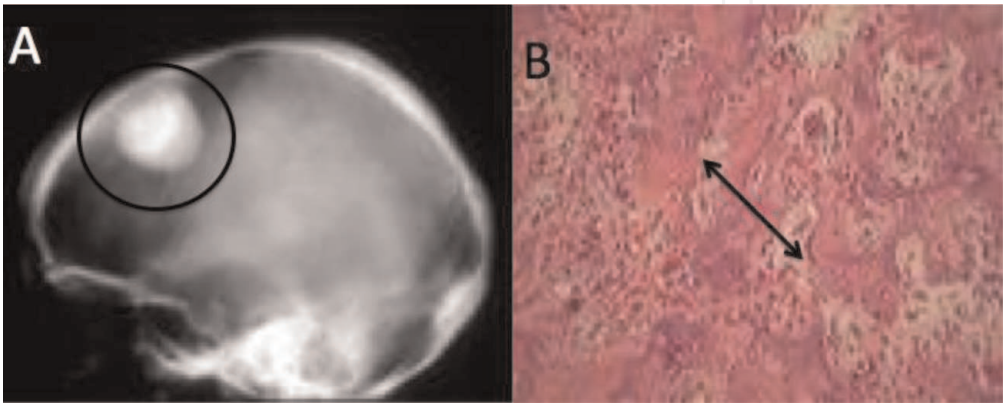


Figure 1.
Radiological aspect of osteoma, (A) shows sharply radiodense lesions (black ring), (B) photomicrograph (H&E 40x) similar to normal cortex, revealing mature bone (arrow), with less stroma and no atypia.

Features	Osteoma	Osteoid osteoma	Ossifying fibroma	Parosteal osteosarcoma
Site and location	Cortex of metaphysis (skull, facial bone)	Metaphysis	Metaphysis of the same bones	Metaphysis of long bone
Age in years	40–60 more in males	10–20 more in males	1–70 (wide range), and more in females	30–60 year (older age)
Clinical symptoms	No pain	With pain	No pain	Pain
Radiology	Well-circumscribed radiodense and without destructive features	A single <1.5 cm nidus that may be radiolucent or ossified and surrounded by a reactive bone	Well-demarcated radiolucent in the early stages and then progressive calcification	Continuity with the medullary component of the parent bone is not present. Appears to be attached to the surface of the parent none
Histology	Nodular or dome-shaped, dense cortical bone Consists of dense lamellar bone with or without Haversian canals and usually without a medullary component Medullary component consists of hematopoietic or fibroadipose tissue Regular large ossicles of mature bone	Lamellar bone with prominent osteoblastic rimming Osteoma may have focal areas of reactive bone with similar features but not cellular as compared to OO, see also (Table 3)	The stroma is fibrous and more cellular Small ossicles and irregular bony trabeculae, much less mature bone Psammoma bodies	Tumor osteoid is arranged in parallel arrays and separated by a bland fibroblastic stroma. With minimal atypia. Cartilage may be seen. Genetically, amplification of 12q ¹³⁻¹⁵ seen with CDK4 and MDM2 genes. See also (Table 9) No other benign lesions seen (See Table 9)

Table 2.
Differential diagnosis of osteoma with osteoid osteoma, ossifying fibroma, and parosteal osteosarcoma.

3. Osteoid osteoma

It is a benign tumor of medullary metaphysis origin with a <2 cm lucent nidus, encompassed by the solid periosteal reaction. The characteristic features are its association with nocturnal pain (due to release of prostaglandin via Cox-1 and Cox-2 pathway) which can be relieved by aspirin, a salicylate analgesic. Histologically it comprised of three zones, nidus, fibrovascular stroma, and mineralized sclerotic bone. The nidus is composed of interconnected newly formed blood vessels and new bone-forming cells (osteoblasts and osteoid) [5–7] (Table 3, Figure 2). These tumors should be differentiated from osteomyelitis, stress fractures, osteblastoma, osteosarcoma, and other lesions [8, 9].

4. Osteblastoma

It arises from the medullary metaphysis, but most cases arise from spongiosa of the bone. It is a rare benign tumor of the bone. These tumors are now considered in intermediated groups as they may be locally aggressive and tend to affect the axial skeleton more often than osteoid osteoma. They are less painful and have poor response with aspirin [10, 11]. These have many osteoclasts like giant cells and less

Features	Osteoid osteoma	Osteomyelitis	Stress fracture	Osteoblastoma	Ossifying fibroma	Osteosarcoma
Site and location	Cortex of metaphysis	Not site specific	Not site specific	Medulla of metaphysis	Same bones	Metaphysis of long bone
Age in years	5–30 More in males	Any age	Old age	Mean age 20 (10–73) More in females	Wide range (1–70)	Older age
Clinical symptoms	Severe pain	Pain, fever	Pain	Not severe pain	No pain	Pain
Radiology	A single <1.5 cm nidus that may be radiolucent or ossified and surrounded by a reactive bone	Bone scan demonstrates central area of reduced uptake representing an avascular area of purulent material	Positive findings include sclerosis, periosteal reaction/elevation, cortical thickening, and a fracture line	Well-circumscribed nondestructive but sometimes with secondary ABC changes Some have central nidus >2 cm The lesions are predominantly lytic, with a rim of reactive sclerosis	Well-demarcated radiolucent in the early stages and then progressive calcification	Continuity with the medullary component of the parent bone is not present. Appears to be attached to the surface of the parent bone MRI and CT are more helpful
Histology	Irregular trabeculae of lamellar bone with prominent osteoblastic rimming Loose fibrovascular stroma See also (Table 2)	No central nidus Presence of neutrophils, lymphocytes, macrophages, etc. (acute or chronic inflammatory cell infiltrate)	Zonal pattern with central, more mature, denser bone and peripheral woven bone Cartilage with endochondral ossification may be present	Irregular anastomosing trabeculae of osteoid and woven bone Variable mineralization and thickness of woven osteoid trabeculae. No central maturation like nudus Intralesional hemorrhages like ABC and numerous osteoclast-like giant cells No peripheral rim of fibrovascular tissue like in nidus Epithelioid aggressive variant with large atypical epithelioid like osteoblasts may confuse with OS, but take guidance from radiology. See (Tables 2 and 4)	The stroma is fibrous and more cellular Small ossicles and irregular bone Trabeculae, much less mature bone Psammoma bodies	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in OS Lacks the fibrovascular stroma and osteoblastic rimming of osteoid osteoma May show cartilage component. See (Tables 4–8) for IHC

Table 3.
Differential diagnosis of osteoid osteoma with osteomyelitis, stress fracture, osteoblastoma, ossifying fibroma, and osteosarcoma.

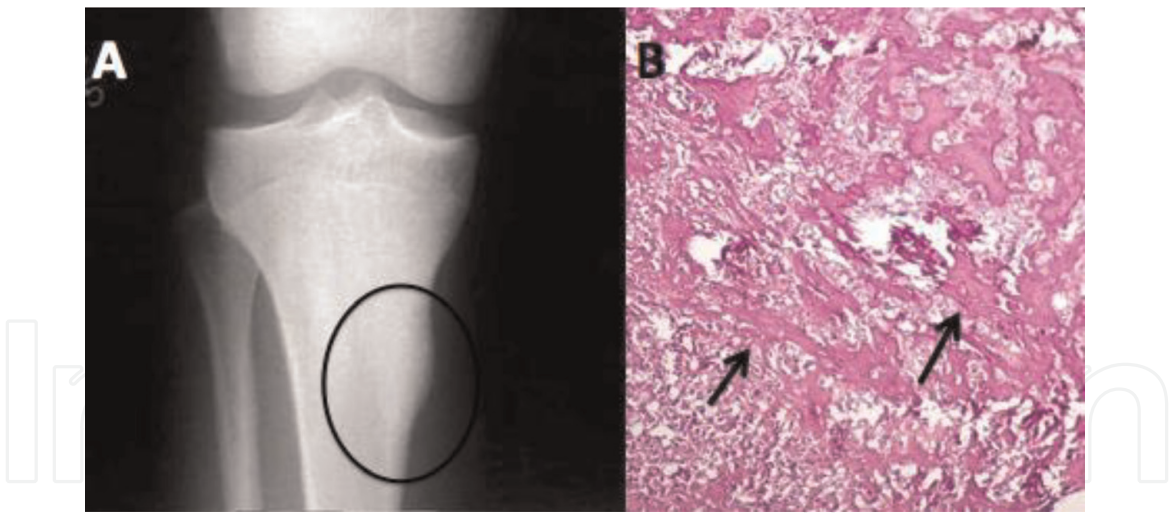


Figure 2.
Radiology of the osteoid osteoma (A) shows sharply radiodense lesions with nidus (black ring), similar to normal cortex, (B) photomicrograph (40X) of osteoid osteomas reveals irregular trabeculae of lamellar bone with prominent osteoblastic rimming and loose fibrovascular stroma (arrows).

Features	Osteoblastoma	Osteoid osteoma	Osteosarcoma	Giant cell tumors	Aneurysmal bone cyst (ABC)
Site and location	Medulla of metaphysis	Cortex of metaphysis	Metaphysis	Metaphysis of epiphysis	Diaphysis
Age in years	Mean age 20 (10–70) More in females	5–30 More in males	10–25	>20 Up to 40	Younger 10–20
Clinical symptoms	Not severe pain	Severe pain	Pain	No pain	No pain
Radiology	Well-circumscribed nondestructive but sometimes with ABC changes Some have central nidus >2 cm. The lesions are predominantly lytic, with a rim of reactive sclerosis	A single < 1.5 cm nidus that may be radiolucent or ossified and surrounded by a reactive bone	Radiographically, osteosarcoma is poorly circumscribed with cortical destruction and evidence of periosteal reactive bone Permeative pattern of growth at the periphery	Soap bubble appearance	Lytic but demarcated Both processes may have similar presentations and radiographic findings and tend to involve the vertebra
Histology	Irregular anastomosing trabeculae of osteoid and woven bone Variable mineralization and thickness of woven osteoid trabeculae. No central maturation like nidus Intralesional hemorrhages like ABC and numerous osteoclast-like giant cells No peripheral rim of fibrovascular tissue like in nidus	Irregular trabeculae of lamellar bone with prominent osteoblastic rimming Loose fibrovascular stroma	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma. Atypia is common The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in OS Lacks the fibrovascular stroma and osteoblastic rimming of osteoid osteoma May show cartilage component	Sheets of giant cells and more in number and contain more nuclei Giant cell tumors contain mononuclear stromal cells	Small foci of reactive osteoid may be present in aneurysmal bone cysts, which should not be confused with osteoblastoma

Table 4.
Differential diagnosis of osteoblastoma with osteoid osteoma, osteosarcoma, giant cell tumors, and ABC.

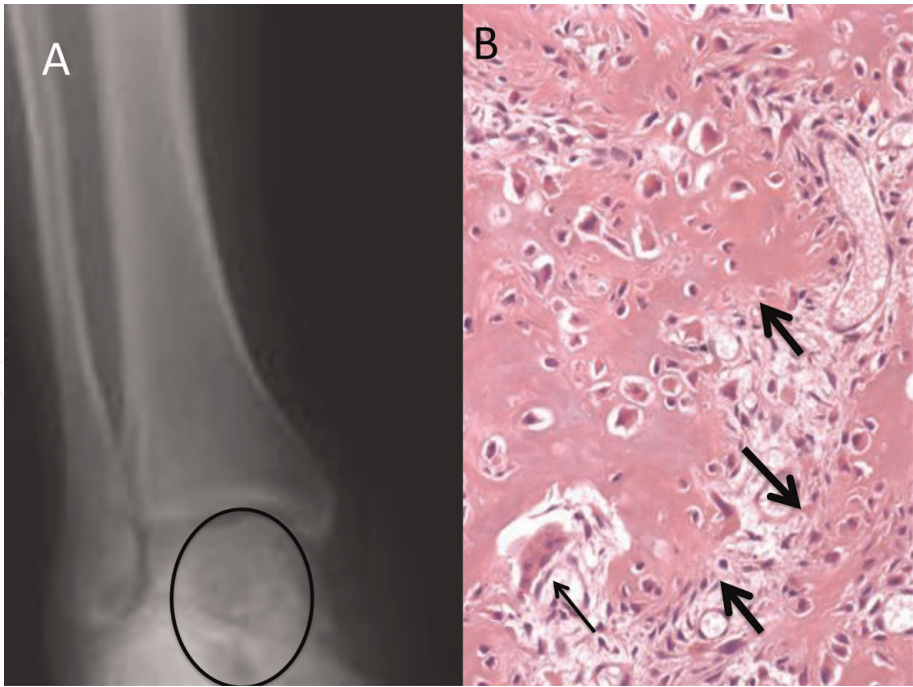


Figure 3.
(A) Radiology (left ankle bone) shows osteoblastoma, with well-circumscribed nondestructive but sometimes with ABC changes (ring). The lesions are predominantly lytic, with a rim of reactive sclerosis.
(B) Photomicrograph (H&E 40X) showing irregular anastomosing trabeculae of osteoid and woven bone, variable mineralization, and thickness of woven osteoid trabeculae (thick arrows). Numerous osteoclast-like giant cells (thin arrow). No peripheral rim of fibrovascular tissue like in nidus.

rimming with osteoblasts, osteoid, and rich vascularity as compared to osteoid osteoma (Table 4, Figure 3) [6, 12, 13]. This is also called giant osteoid osteoma more than 2 cm in size; it does not have the surrounding reactive bone as compared to osteoid osteoma and is not associated with nocturnal aches [13].

4.1 Aggressive osteoblastoma

It is a rare variant of osteoblastoma, which commonly arises from the vertebrae, long bones, and bones of jaws; it is characterized by the presence of epithelioid osteoblasts in the stroma with aggressive behavior. The tumor has propensity for local invasion and recurrence, but still no metastasis has been seen in any case in the literature [14, 15].

5. Osteosarcoma (OS)

It is the most common primary bone tumors (20%) of mesenchymal origin second to multiple myeloma; the main histologic feature of this tumor is direct production of malignant osteoid from malignant cells without normal osteogenic process through fibrous and cartilage way; the cartilage or fibrous tissue may present elsewhere or in other osteogenic portions. Malignant osteoid is the characteristic finding of all types of OSs, and it is a eosinophilic, homogenous, glassy appearing lacelike material [16, 17].

Osteosarcoma is very rare in young children (0.5 cases per million per year in children <5 years). However, the incidence increases steadily with age [13].

It can affect all ages, but 75% appears in young age, it can affect all bones most commonly in metaphysis of long bones, and knee joint is commonly involved

(60%). There is no gender difference, but males are affected more as compared to females [13].

There are many morphological variants of OS with anastomosing, reticular osteoid and oval, spindled to epithelioid stromal cells. The cells may form rosettes to small sheets in different patterns. There are several subtypes of OS, which can be, differentiated on the basis of the site, degree of histological differentiation, and association with underlying disease [12, 13, 16, 17].

5.1 Conventional intermedullary OS

This type of OS shows the male predominance and bimodal age, pediatric and adult sarcoma. It has some association with hereditary effect, e.g., with mutation of RB gene, Li-Fraumeni syndrome, Ollier disease, fibrous dysplasia, and Paget disease (secondary OS). Radiation also plays a role in its pathogenesis. The long bones are commonly involved showing classical “Codman triangle” to moth-eaten picture due to permeation and destruction of medullary as well as cortical bone on radiology [18, 19].

It is composed of hyperchromatic cells forming sarcomatous component around the classical osteoid (**Figure 4**). This comprised of chondroblastic OS (25%), fibroblastic OS (25%), and osteoblastic OS (50%). Other subtypes are small cell-type OS, giant cell-rich OS, telengiactatic-type OS, surface-type OS, periosteal OS, and parosteal OS. Histologically it has two grades, low- and high-grade OS. Immunohistochemistry has some role in its differentiation from cartilage and other bone tumors, i.e., ALK, VIM, variable SMA, and desmin. The S100 is always negative except there is chondroid differentiation. EMA and keratin are negative in tumors [16, 20–23].

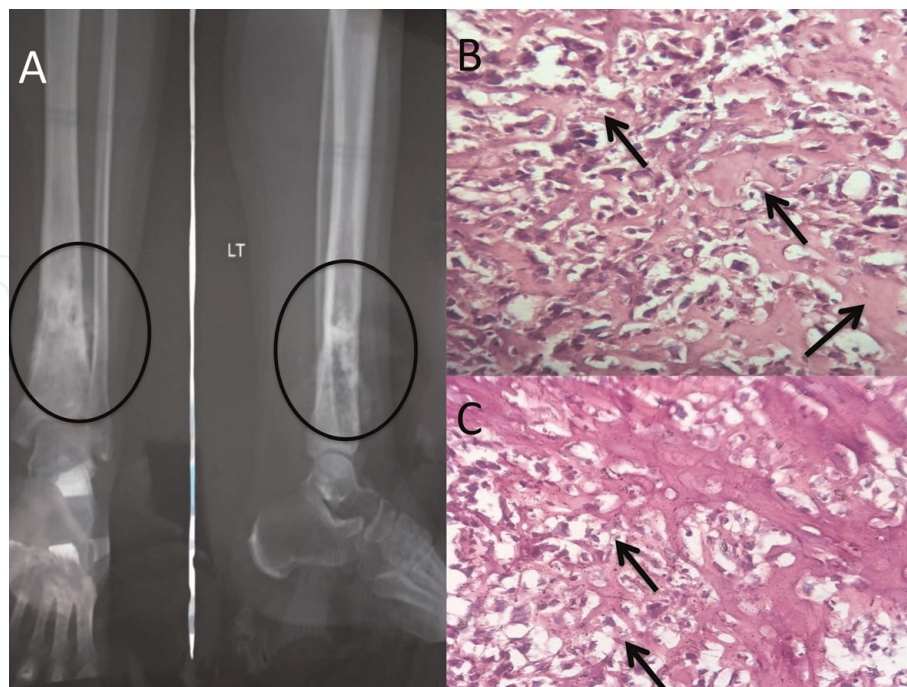


Figure 4. Radiological examination (A) showing intramedullary OS of left lower tibia with osteolytic and sclerotic lesion in lower end above ankle joint (rings). There is a medullary and cortical destruction of bone. The photomicrograph of (B & C) (40X with H&E) based characteristic of conventional osteosarcoma, is the identification of osteoid (arrows), which is a dense, pink, amorphous extracellular material containing large amounts of collagen type I. (C) The tumor cells (atypical osteoblast) and cytoplasm are eosinophilic, are larger than normal osteoblasts (arrows), and vary in size with nuclear atypia.

6. Differential diagnosis of conventional OS

6.1 Fracture callus and stress fracture

Sometime fracture callus may be confused with OS, because there is formation of spindle cells and cartilage with new bones, but all these elements are arranged with orderly maturation as compared to haphazard and abrupt arrangement in OS (Table 5). Postmenopausal women may have insufficiency fractures in the pelvis resembling metastatic carcinoma [24, 25].

The osteoid and maturation level are the main difference between two lesions. The osteoid of the callus woven bone is mature and shows a parallel pattern with prominent osteoblastic rimming. Malignant osteoid is a eosinophilic, amorphous, fibrillary deposit between individual tumor cells or group of tumor cells. There are

Features	Conventional osteosarcoma (NOS)	Fracture callus	Ewing’s sarcoma	Giant cell tumors (GCT)	Chondroblastoma
Site and location	Long bone	Not specific Can be of any site and any bone	Medulla of diaphysis and metaphysis	Metaphysis and epiphysis Rarely in vertebrae body	Epiphysis
Age in years	10–25	Any age	Children 4–20	>20 up to 40	Younger age 10–30
Clinical symptoms	Pain	May be pain		No pain	Pain
Radiology	Radiographically, osteosarcoma is poorly circumscribed with cortical destruction and evidence of periosteal reactive bone Permeative pattern of growth at the periphery	There may be increased translucency of the fracture during this stage, due to bone resorption	Metaphyseal or diaphyseal tumor with a predominantly lytic appearance. No bone matrix is radiographically identified Onion skin appearance in ES on radiology	Soap bubble appearance	Sharp and lytic lesions Fine calcification
Histology	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular osteoblastic stroma. Atypia and mitosis are common The small cells between bony osteoid. CD99, LCA, CK, and S-100 are negative	There is spindle cell proliferation with cartilage and bone, but orderly maturation is present in fracture callus and stress fractures	Small round blue cells with regular size, primitive-appearing cells t(11;22)(q24;q12) chromosome rearrangement and CD99+ve	Sheets of giant cells and mononuclear stromal cells	Benign-appearing chondrocytes, without osteoid differentiation Nuclear grooves Chicken wire vascular stroma

Table 5.
Differential diagnosis of conventional osteosarcoma (NOS), fracture callus, Ewing’s sarcoma, GCT, and chondroblastoma.

two types of tumor osteoid, early-tumor osteoid, lacelike pattern around tumor cells, and late-tumor osteoid, a mineralized one having an appearance of a woven bone, but an important feature is that tumor osteoid is not rimmed by osteoblasts [16].

6.2 Osteomyelitis

Osteomyelitis is an important cause of morbidity and mortality in children and adults due to acute and chronic bacterial infection. More common sites are the metaphysis and epiphysis of the lower limbs and vertebrae [26–28].

Primary (hematogenous) osteomyelitis is associated with fever and local painful mass and may have fistula formation. A history of recent trauma with open fracture is significant for secondary osteomyelitis. The radiology and MRI are more helpful in the diagnosis of these lesions [26]. The C-reactive protein and erythrocyte sedimentation rate (ESR) are markedly elevated. Biopsy shows necrotic bone, fibrotic marrow, and chronic inflammation with or without an acute inflammatory component. Reactive bone is usually produced as part of an associated periosteal reaction, readily differentiated using histological features [24] (**Table 6**).

6.3 Osteblastoma

It is a benign osteoid-producing tumor with roughly the same age and sex distribution as osteosarcoma. In conventional radiography, there is a well-defined round expansile mass with central radiolucent zone (>1.5 cm) and a peripheral rim of sclerosis (sclerosis may not be as extensive as in osteoid osteoma). On biopsy, there is an irregular interlacing network of osteoid with prominent osteoblastic rimming and features of woven bone; the differential diagnosis from OS is sometimes difficult when the OS is well differentiated and OB is showing bizarre osteoblasts due to degenerative activities [24] (**Table 4**).

6.4 Aneurysmal bone cyst (ABC)

ABC has the same age range and location as osteosarcoma. It presents with pain and occasional pathological fracture. Secondary aneurysmal bone cysts can be seen in older patients, superimposed on other primary neoplasms. Conventional radiographs show radiolucent expansile bone lesion. MRI shows fluid levels on T2-weighted images. Biopsy can differentiate from telangiectatic osteosarcoma (TOS), which displays obvious histological features of malignancy (marked cellular pleomorphism, high and abnormal mitotic activity) (**Figure 5**) [24, 29] (**Table 7**).

6.5 Fibrous dysplasia (FD)

It is a nonneoplastic intramedullary condition, associated with two forms, monostotic (seen in the ribs, femur, and tibia in young adults) and polyostotic (endocrine dysfunctions). The presentation of polyostotic fibrous dysplasia commonly includes bone deformity and pathological fracture. It has wide age range at presentation and no gender preference. The radiographs show a fusiform expanded swelling with thinning of cortex not associated soft with tissue mass. There are generally no aggressive radiographical features. Pathological fracture may be seen [24].

Microscopically, there are curved and irregularly shaped trabeculae-like fish-hook configuration. These are interspersed in fibrous stroma of variable cellularity. These poorly mineralized bony trabeculae have no rimming of osteoblasts, and cartilaginous islands are present in 10% of cases [30].

Features	Osteosarcoma	Osteomyelitis	Langerhans granuloma	Fibrous dysplasia
Site and location	Long bone	Epiphysis (neonates) Metaphysis (children)	Metaphysis or diaphysis	Medulla of diaphysis
Age in years	10–25	Any age, more in children	More common in children 5–15 years	1–30 years > males
Clinical symptoms	Pain	Pain, fever, discharges	Local pain	No pain
Radiology	Radiographically, osteosarcoma is poorly circumscribed with cortical destruction and evidence of periosteal reactive bone Permeative pattern of growth at the periphery	The earliest radiological changes are seen in adjacent soft tissues +/- muscle outlines with swelling and loss or blurring of normal fat planes. An effusion may be seen in an adjacent joint. MRI is more helpful	Multiple lytic lesions with significant periosteal reaction	The conventional radiographs show ground glass appearance with no associated soft tissue mass. There are generally no aggressive radiographical features
Histology	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma. Atypia is common The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in OS Lacks the fibrovascular stroma and osteoblastic rimming of osteoid osteoma May show cartilage component	In acute cases, neutrophils and necrotic bony trabeculae, in TB, granulomas, and in chronic nonspecific cases, lymphocytes and macrophages are more common	There is monoclonal proliferation of Langerhans cells (distinctive cells of monocyte–macrophage lineage) and should be considered a malignancy although its biological behavior is very variable. EM shows Birbeck granules. Express CD1a, S100, HLA-DR	There is large fibrous matrix with scattered curvilinear irregularly shaped trabeculae of immature, inadequately mineralized bone. There is no rimming by osteoblasts GNAS +ve, osteoclastin +ve Run-X-2 +ve, see also (Table 9)

Table 6.
Differential diagnosis of osteosarcoma, with osteomyelitis, Langerhans granuloma, and fibrous dysplasia.

It should be differentiated from other bony lesions, cemento-ossifying fibroma (rimming of osteoblast), chondrosarcoma (binucleation), Paget’s disease (mosaic pattern bone histologically), non-ossifying fibroma (metaphyseal fibrous defect in tibia with the absence of osteoid), simple bony cyst, and osteofibrous dysplasia/ossifying fibroma (exclusively seen in the tibia almost, with anterior bowing of the bone, in the cortex; rimming is seen around lamellar bony trabeculae) [30].

Some immunomarkers are helpful in the diagnosis of FD. Fibroblastic cells in FD and ossifying fibroma show strong Runx2 expression in the nucleus, while osteocalcin is seen in calcified regions in FD, and G protein genes (GNAS) are positive in extragnathic FD. FD shows GNAS (G protein gene) mutation not seen 15 in other lesions. FD is negative for osteocalcin [31, 32] (Table 6).

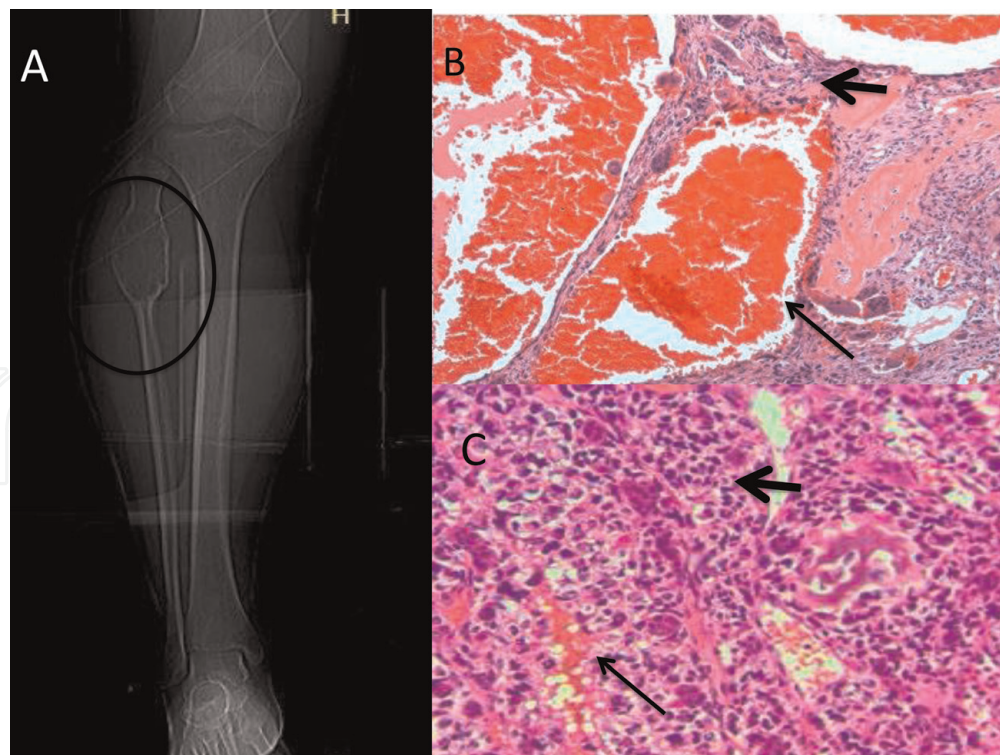


Figure 5.
 (A) Radiological examination of telangiectatic osteosarcoma revealing a lytic/expansile, (ring) permeative lesion in the proximal fibula metaphysis with a wide zone of transition and cortical destruction, (B&C) histological examination of the photomicrographs (B; 5X and C; 400X, H&E) blood-filled spaces (thin arrows), separated by septa containing highly malignant cells (small arrows).

6.6 Ewing's sarcoma

It is the second commonest primary malignant bone tumor of the childhood after osteosarcoma. It typically arises from the medullary cavity and invades the Haversian system. Radiologically, It presents as moth-eaten and destructive permeated lucent lesions in the shaft of the long bones. It appears typical onionskin appendence due to periostitis. It may also involve flat bones and appears sclerotic in up to 30% of cases [33].

Same age range and predilection for males. Type II symptoms (e.g., fever, night sweats) are usually seen. Conventional radiographs show a metaphyseal or diaphyseal tumor with a predominantly lytic appearance. No bone matrix is radiographically identified. Onionskin appearance in ES on radiology. MRI shows a large soft tissue mass.

Biopsy shows small round blue cell tumor with no osteoid production. Cytogenetic and/or molecular studies show the typical translocations/molecular aberrations of Ewing sarcoma family of tumors and help rule out small cell osteosarcoma (a rare subtype of osteosarcoma with very little osteoid production). CD 99 is positive in EWS [6, 33] (Table 5).

6.7 Chondrosarcoma

It is a cartilage-producing sarcoma with these differences with osteosarcoma. It is most common in patients between 50 and 60 years of age and not seen in less than 20 years. The tumor has a predilection for the pelvic bones and a slower growth rate. Conventional radiographs show a lytic lesion centered in the long bone metaphysis, with a permeative growth pattern scalloping the cortex and showing intra-tumoral calcifications, with a flocculent or ring-shaped appearance. The

Features	Telangiectatic osteosarcoma (TOS)	Conventional OS	Angiosarcoma	ABC	Giant cell tumors
Site and location	Metaphysis	Metaphysis	Not specific	Metaphysis Flat bones, vertebrae, long bones	Metaphysis of epiphysis
Age in years	Mean age 20 years	10–25	Old age	Younger 10–20, slightly more in females	>20 up to 40
Clinical symptoms	Dull pain	Dull pain	No pain	No pain	No pain
Radiology	Lytic bony lesions, geographic bony destruction with wide zone of transition tends to be more common than permeative bony destruction	Sclerotic lesions and cortical destruction	Soft tissue mass	Lytic but demarcated Both processes may have similar presentations and radiographic findings and tend to involve the vertebra CT and MRI show fluid level	Soap bubble appearance
Histology	It is consist of vascular sinusoids surrounded by thin septae, osteoid matrix and cells with significant pleomorphism and high mitotic rate	Malignant osteoblasts and malignant osteoids IHC:SATB2 and AKP are positive, TP53 alteration and MDM2 amplification	Blood vessels are lined by malignant endothelial cells	Small foci of reactive osteoid may be present in aneurysmal bone cysts, which should not be confused with osteoblastoma IHC shows rearrangement of USP6, gene present of Ch 17, t(16;17)(q22;p13). Fusion of USP6 with CDH11	Sheets of giant cells and mononuclear stromal cells. Sometimes, may appear with blood-filled spaces

Note: ABC; Aneurysmal bone cyst, GCT; Giant cell tumors, OS; Osteosarcoma, IHC; Immunohistochemistry, Ch; chromosome.

Table 7.
Differential diagnosis of telangiectatic osteosarcoma (TOS) and, conventional osteosarcoma, angiosarcoma, ABC, and GCT.

cortex is usually thickened with a slightly expanded fusiform appearance, mainly due to the slow permeative growth of the tumor (chronic periosteal reaction). Scalloping of the inner cortex is a radiographic sign worrisome for malignancy. Biopsy is the confirmatory test. Low-grade CS with ossification may mimic OS, but the cartilaginous component in OS, if seen, is always high-grade and malignant osteoids are essential for its diagnosis. Dedifferentiated CS has a well-differentiated benign chondral lesion or chondrosarcoma and sharply juxtaposed with a high-grade non-cartilaginous component; typically, there is an abrupt transition between the two tissue types. The non-cartilaginous component of dedifferentiated chondrosarcoma is generally osteosarcoma, a fibrosarcoma, or a malignant fibrous histiocytoma. Dedifferentiation to leiomyosarcoma, giant cell tumor, and, rarely, clear-cell chondrosarcoma or rhabdomyosarcoma has been reported. Always look the age, site and radiology for help. The S-100 is negative in OS [34].

6.8 Giant cell tumor (GCT) of the bone

The GCT is usually benign and arises from long bone epiphysis and metaphysis. It is rare in vertebrae, but when they occur in a vertebra, the body and not the arch is usually involved [35]. The pathogenesis of GCT is accredited due to

overexpression of a tumor necrosis factor receptor (RANK/RANKL) which results in a hyper-proliferation of osteoclasts [16]. Histologically, the GCTs are characterized by the presence of osteoclast-like, giant cells and round-to-oval polygonal mononuclear cells. Frequent mitotic figures in the mononuclear cells may be seen, especially in pregnant women or those on the oral contraceptive pill (due to increased hormone levels) [16, 35]. Important features are given below (**Table 5**).

This lesion is most common in skeletally mature women with closed epiphysis which usually presents with bone pain and sometimes pathological fractures. It involves epiphysis and extends to joint articular cartilage. Conventional radiographs show tumor with an osteolytic appearance located in the epiphysis of long bones, with the distal femur and proximal tibia being the most commonly affected. No doubt it is benign but is locally aggressive. This translates radiographically into the absence of an osteosclerotic rim at its periphery as well as the presence of a soft tissue mass. No bone/osteoid formation is identified. Radiology is soap bubble appearance. Biopsy shows typical appearance of evenly distributed giant cells in a mononuclear stroma. The nuclei of the giant cells resemble the nuclei of the histiocytes. There is atypia or mitosis, potentially malignant with 50% recurrence rate and 10% metastasis [32].

6.9 Primary lymphoma of the bones

These are rare manifestation than secondary lymphoma involving the bone. It is rare, accounting for <5% of bone tumors and <1% of non-Hodgkin lymphoma. It is more common in old age males as compared to OS. The patient presents with type II general symptoms like night sweatings, fever, and weight loss. The conventional radiographs may be normal (tumor cells tend to grow between patient's bony trabeculae with little bone destruction). There may be multiple or single bone involvement. MRI shows focal change in the marrow signal. Bone marrow biopsy is usually the confirmatory test. Flow cytometric studies should be considered in patients suspected of having lymphoma. Leukocyte common antigen (LCA) is positive in lymphomas while negative in OS [24, 36]. Usually it should be differentiated from infections, small cell OS, Ewing's sarcoma, eosinophilic granuloma, and metastatic lesions [36, 37].

6.10 Langerhans cell histiocytosis

It is a multisystem but rare disease. It is associated with a wide and heterogeneous clinical spectrum and extent of multisystem involvement. The age range is 5–15 years, more common in the children and early teens. The males are more affected than females (M/F ratio is 3:2) [38, 39]. It has a predilection for the bones of the skull, the calvarium, but any other bone like the humerus, femur, and ribs can be involved. There is local pain and swelling. Radiographically there are multiple lytic lesions with significant periosteal reaction. Biopsy shows a proliferation of neoplastic Langerhans cells in an inflammatory background [24] (**Table 6**).

6.11 Metastases from other malignancies

Generally it occurs in older age group than osteosarcoma. There is usual history of a primary malignancy known to metastasis to bone, such as breast, lung, thyroid, kidney, and prostate. Conventional radiographs and radionuclide scans usually show osteolytic lesions (rarely osteoblastic) involving multiple bones. CT imaging may reveal other organs affected by metastatic disease. Biopsy usually confirms the diagnosis [35].

7. Special variants of OS with differential diagnosis

7.1 Telangiectatic OS

It is an uncommon variant of OS in the second decade with a mean age of 20 years. It comprises of 2.5–12% of all osteosarcomas. Almost all osteosarcomas have telangiectatic component. In order to diagnose telangiectatic osteosarcoma, there should be more than 90% component with telangiectatic features. It is more common in males like conventional OS (with a ratio of 2:1 for male to female) [24] better than conventional OS [13].

Multiple cyst-like spaces resemble an aneurysmal bone cyst, except that the septa of the cysts contain stromal cells (mononuclear and multinucleated) with cytologically malignant changes. Mitotic figures are present, including atypical forms. Sometimes the malignant stromal cells are floating in the center of the large hemorrhagic cysts; identification of the stromal cells may be difficult, requiring multiple sections. The TOS may arise in other bony diseases like fibrous dysplasia, Paget's disease, or postradiation therapy. Malignant osteoid can be difficult to identify, usually focal and found in a delicate lacelike pattern [24, 40] (**Figure 5** and **Table 7**).

Advice: If the diagnosis of aneurysmal bone cyst is being considered, all tissue should be evaluated histologically for evidence of malignant stroma to rule out telangiectatic osteosarcoma radiological correlation.

7.2 Differential diagnosis of TOS

7.2.1 Aneurysmal bone cyst

The aneurysmal bone cysts are usually seen in young age with slight female preponderance in flat and vertebral areas but may involve long bones. Radiology shows a lucent expansile lesion in the metaphysis of long bones with thin reactive covering of periosteal bone. CT and MRI show some fluid levels in the ABC. Microscopically, thin blood filled spaces. These spaces are not lined by endothelium but only fibroblastic cells are there. The stroma of the ABC may be cellular but typically lacks cytological atypia and atypical mitoses and may contain reactive bone with atypical osteoblasts. Cytologic malignant features and atypical mitoses are absent (**Figure 6**, **Table 7**).

7.2.2 Conventional osteosarcoma

Radiographically, these tumors are not purely lytic. Intramedullary osteosarcoma may contain focal telangiectatic areas, which should not be overinterpreted (**Table 8**).

7.3 Well-differentiated intraosseous low-grade osteosarcoma

The low-grade OS is a rare subtype of osteosarcoma, usually occurring in young adults in their tibia and femur. Microscopically, there may be components of heavy osteoid and fibrocollagenous stroma, and the cells appear benign but with invasion of cortex and surrounding soft tissue. The spindle cells are with mild atypia, marked collagen production, scant atypia, and abundant osteoid production (**Figure 9**). The patients present with pain and swelling in older people. It arises from metaphysis of long bone of lower extremity, while other sites are uncommon. Radiologically, there are irregularly sclerotic lesions with poorly defined sclerotic margins, and mineralized matrix is common (**Figure 7A–C**).

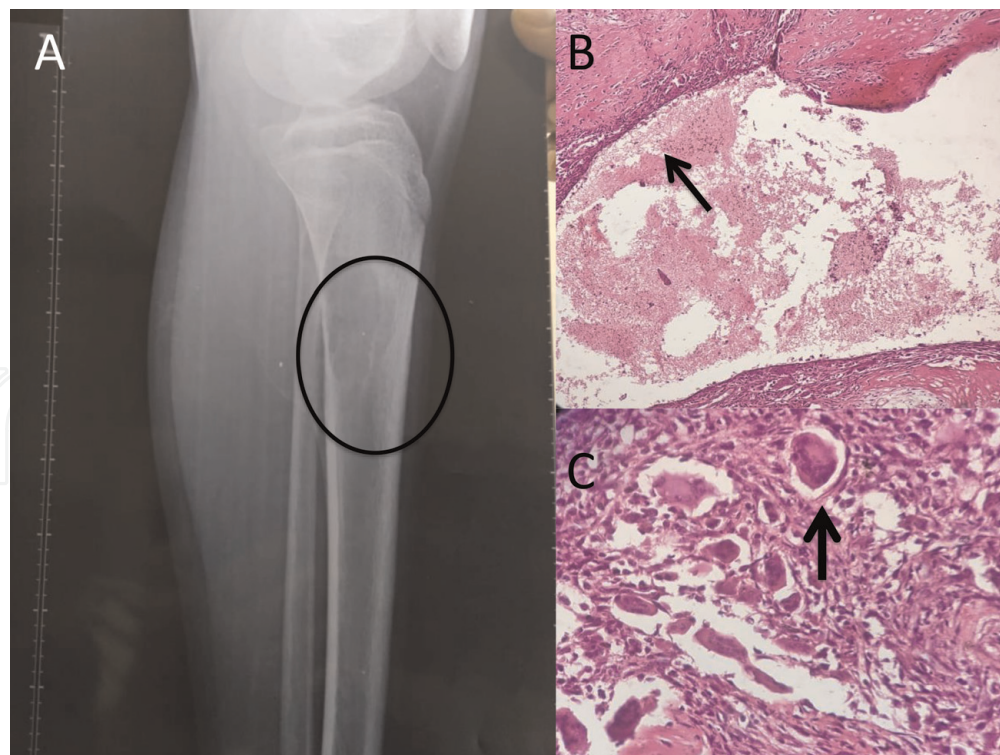


Figure 6.
 (A) Radiological examination reveals (ring) homogenous cystic areas (aneurysmal bone cyst) without cortical destructions. (B) Photomicrograph (H&E 10X) revealing cystic lesions (arrow), with giant cells (red arrow) separated by fibrous septa (black arrows), alternating with solid areas and septa lined by fibroblasts, myofibroblasts, and histiocytes but not endothelium (C).

7.4 Differential diagnosis of well-differentiated OS

7.4.1 Chondroblastoma

Chondroblastoma is a rare primary bone tumor of young people that typically arises at the ends of the long bones. Radiologic investigations show a small, circumscribed, lytic lesion. The tumor is characterized histologically by the proliferation of chondroblasts along with areas of mature cartilage, giant cells, and, occasionally, secondary aneurysmal bone cyst formation. Chondroblastoma, however, may also present with atypical features, such as prominent hemosiderin deposition, numerous giant cells, or the presence of a large aneurysmal bone cyst component.

A rare variant of osteosarcoma with CB features may be seen and can be difficult to distinguish from CB, as both tumors can present in young patients as a lytic lesion in an epiphyseal location. Histologically, this OS may reveal small round-oval cells with eosinophilic cytoplasm and scattered giant cells and therefore may cause confusion with CB, especially on a small biopsy specimen. Clues to the appropriate malignant diagnosis include a more aggressive, infiltrative lesion on radiological studies, and the presence of nuclear atypia, atypical mitoses, and/or malignant osteoid production on histologic examination (Table 5).

7.4.2 Fibrous dysplasia

It is usually seen in young ages (10–30 years) and more common in males. It is commonly found in metaphysis, diaphysis of ribs, jaw, skull, tibia, and femur. It is locally aggressive tumor and may be monostotic or polyostotic and associated with

Features	Osteosarcoma	MFH	Lymphoma	Osteoblastoma
Site and location	Metaphysis of long bone	Metaphysis of the long bones	Metaphysis	Metaphysis
Age in years	10–25	10 to 60, commonly seen in the second decade	50–60	Younger age and more in females 10–30
Clinical symptoms	Pain	Dull pain but may be associated when arising from other primary bone lesions, like Paget’s disease, radiation, giant cell tumor, and bone infarction	Localized pain and swelling	Pain
Radiology	Radiographically, osteosarcoma is poorly circumscribed with cortical destruction and evidence of periosteal reactive bone Permeative pattern of growth at the periphery	Purely osteolytic permeative lesions without a periosteal reaction and without mineralization	The most common is a lytic pattern with permeative bone destruction and a wide zone of transition	Well-defined lytic lesions
Histology	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma. Atypia is common The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in OS Lacks the fibrovascular stroma and osteoblastic rimming of osteoid osteoma May show cartilage component	No extensive osteoid formation. Some osteoid osteogenic sarcomas may have a predominant histologic pattern of malignant fibrous histiocytoma; the presence of osteoid formation requires the diagnosis of osteosarcoma They are heterogeneous fibroblastic tumors formed by poorly differentiated fibroblasts, myofibroblasts, histiocyte-like cells with high degree of pleomorphism and characteristic storiform pattern and also demonstrating bizarre multinucleated giant cells Run-X-2 negative	DLBCL is the most common subtype. The bony pelvis and femur are the most common locations	They manufacture abundant osteoid, but they are not composed of atypical and pleomorphic osteoblasts

DLBCL; Diffuse large B cell lymphoma, MFH; Malignant Fibrous Histiocytoma.

Table 8.
Differential diagnosis of osteosarcoma with malignant fibrous histiocytoma, lymphoma, and osteoblastoma.

endocrine disorders. Radiologically, it is circumscribed radiolucent lesions, within the medullary cavity.

There are irregularly shaped bony trabeculae without rimming of osteoblasts.

The osteoids are of mature woven bones, and irregular in FD, while mature osteoids are present in WDIOS. There is no cortical destruction on X-rays seen in

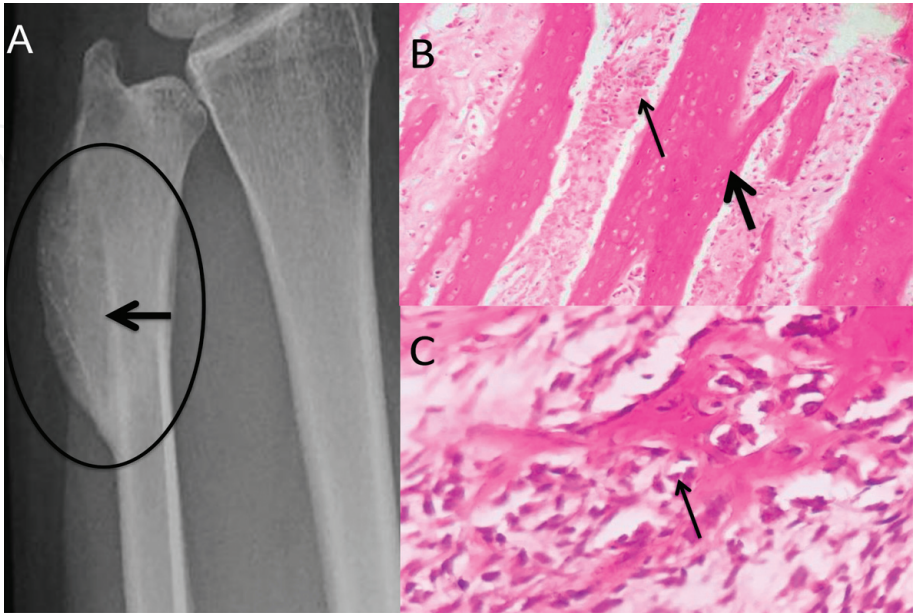


Figure 7.
(A) Radiological examination showing medullary and cortical bone destruction wide zone of transition (ring and arrow), permeative or moth-eaten appearance. (B) Photomicrograph of (10X H&E) of conventional **intramedullary osteosarcoma** and bony osteoid (thick arrow) surrounded by pleomorphic stroma and mitoses (thin arrows) (20X H&E) (C).

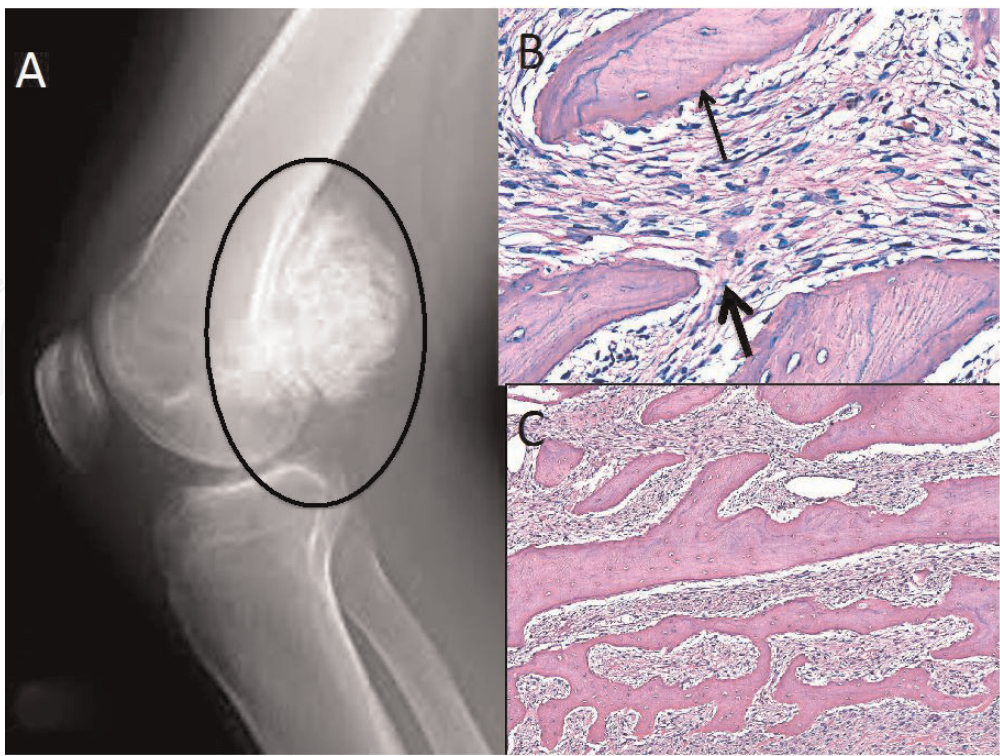


Figure 8.
X-ray of **parosteal osteosarcoma** (ring) showing surface-attached mass (A). Photomicrograph (H&E 20X) revealing continuously branching bony trabeculae (thick arrow) with spindle cell proliferation of malignant cells (thin arrow) (B and C).

FD, while there are irregularly sclerotic lesions with poorly defined sclerotic margins. The mineralized matrix is common in WDIOS while lacking in FD (Tables 6 and 9).

7.4.3 Non-ossifying fibroma (cortical fibrous defect)

Usually seen in young persons, it is a benign lesion. Microscopically, no osteoid and bony trabeculae but only storiform spindle stroma, giant cells, and hemosiderin-laden microphages are seen. Radiologically, these are eccentric sharply defined lytic lesions in metaphyseal cortex in young people.

7.4.4 Parosteal osteosarcoma (PAOS)

This infrequent variant occurs in a juxtacortical position in the metaphyses of long bones and grows very slowly. It grows, as a lobulated mass around the bone shafts as a low-grade malignant bone tumor with well-formed bony trabeculae,

Features	WD intramedullary OS	PAOS	COS	PEOS	Fibrous dysplasia
Site and location	Metaphysis	Metaphysis	Metaphysis	Metaphysis	Medulla of diaphysis.
Age in years	10–20	10–25	10–25	10–25	1–30 years > males
Clinical symptoms	Pain and swelling, patients older	Dull pain	Dull pain	Dull pain	No pain
Radiology	Irregularly sclerotic lesions with poorly defined sclerotic margins, mineralized matrix common	Radiodense, bosselated, or mushroom-shaped mass arising on the surface of a bone; in long-term lesions, tumor may encircle the bone	Diffuse cortical destruction like Codman’s triangle, osteoblastic features	Broad-based surface soft-tissue mass causing extrinsic erosion of thickened underlying diaphyseal cortex and perpendicular periosteal reaction extending into the soft-tissue	The conventional radiographs show ground glass appearance with no associated soft tissue mass. There are generally no aggressive radiographical features
Histology	Heavy osteoid component, fibrocollagenous stroma with minimal atypia	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma that exhibits minimal cytologic atypia and minimal mitotic activity without atypical forms	This is a higher-grade osteosarcoma involving the medullary cavity. Periosteal osteosarcoma does not involve the medullary cavity	Osteosarcoma with prominent cartilaginous component. The cartilage in lobules with peripheral spindling and central bone formation. Malignant osteoid/ bone is present but may be focal	There is large fibrous matrix with scattered curvilinear irregularly shaped trabeculae of immature, inadequately mineralized bone. There is no rimming by osteoblasts differentiating feature from cement-ossifying fibroma. Cartilaginous islands are present in 10%, differentiating feature from chondroblastoma

Note: Well-differentiated intramedullary osteosarcoma (WDIOS), parosteal osteosarcoma (PAOS), fibrous dysplasia (FD), conventional osteosarcoma (COS).

Table 9.
Differential diagnosis of WD intramedullary osteosarcoma, parosteal osteosarcoma, conventional OS, periosteal osteosarcoma, and fibrous dysplasia.

osteoid, variable cartilage, and highly fibrous spindle cell stroma in disorganized manner. In some cases there may be hypocellularity, but there is always mild atypia in the stroma. These tumors have a slight female predominance, with a male-to-female ratio of 1:1.5, and occur predominantly in the third decade. About three fourths of cases involve the distal posterior femur, with the proximal tibia as the second most common site. Clinically it presents as a painless mass of long duration; pain may occur late in the course of this tumor but is not evident initially. Microscopically, there is disorderly arrangement of well-formed bony trabeculae and osteoid and exceptionally osteoclast-like giant cells. There are spindle-shaped stroma with mild atypia and variable amount of cartilage (**Table 9**) compared to conventional OS (**Figure 8** and **Table 9**). Radiodense, bosselated, or mushroom-shaped mass arises on the surface of a bone; in long-term lesions, tumor may encircle the bone [41].

7.5 Differential diagnosis PAOS

7.5.1 Osteochondroma

It is a benign disorder where the medullary spaces contain adipose tissue or marrow hematopoietic tissue with cartilaginous cap. The bony trabeculae are normally arranged as compared to the PAOS.

7.5.2 Myositis ossificans

The myositis ossificans (MO) is distinguished from PAOS by its orderly pattern of maturation. Radiologically, things appear inverse in the MO as compared to PAOS. There is the dense ossification in the center in MO and opaque bone at the periphery, making it eggshell in appearance. Histologically there is zonal arrangement. Maturation toward lamellar bone and marrow adipose tissue begins

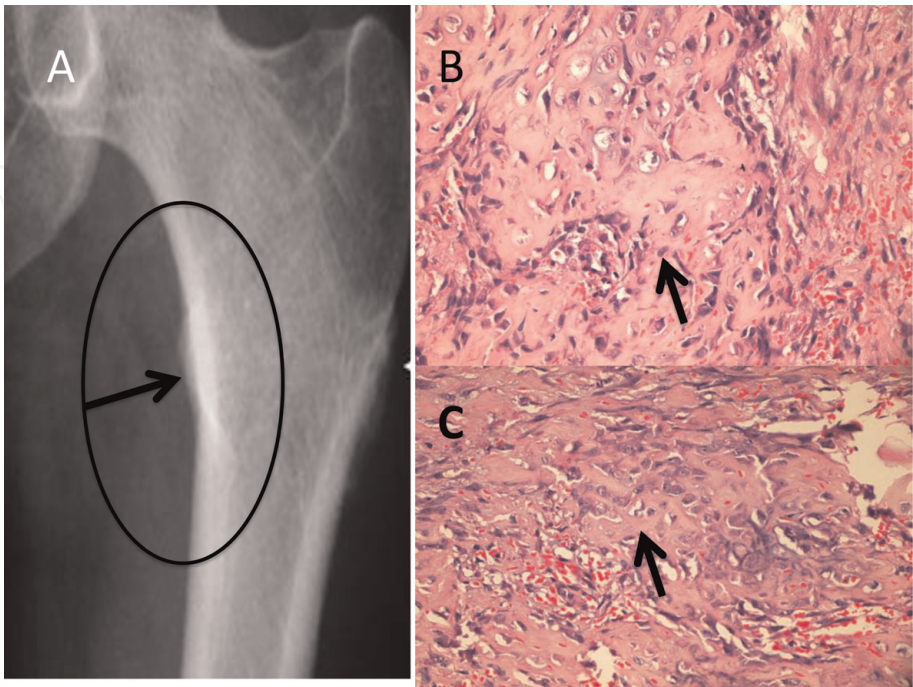


Figure 9.
X-ray of periosteal osteosarcoma (ring) showing broad-based lesion thickening of cortical areas of the femur (A). Photomicrograph (H&E 40X) revealing bony trabeculae with spindle cell proliferation (arrow) of malignant cells and cartilage (red arrow) differentiation (B and C).

peripherally and extends centrally in this proliferative process, which is the reverse in parosteal osteosarcoma [41].

7.5.3 Osteochondroma

The osteochondroma shows continuity of corticomedullary areas of the tumor and the underlying medullary canal, but these features are lacking in PAOS. Medullary spaces contain adipose tissue or marrow hematopoietic tissue, cartilaginous cap.

7.5.4 Periosteal osteosarcoma

Abundant cartilage is present. Higher-grade osseous component and evidence of periosteal reaction.

7.5.5 Periosteal osteosarcoma (PEOS)

This malignant bone tumor is commonly seen in routine biopsies, entirely different from PAOS (juxtacortical OS) despite its similarity with terminology. It arises on surface of long bones (upper tibia and femur). The PEOS affects a slightly older age group (10–20 years) as compared to conventional osteosarcoma. Malignant osteoid must be present, but the predominant pattern of tumor is represented by lobulated chondromatous tissue with cytologic features of grade 2 or 3 chondrosarcoma. Tumor is located on the surface of the bone and may extend into soft tissue. The lesions are limited to the cortex and rarely invade the medullary cavity. The tumor appears perpendicular to the shaft. Sometimes high-grade anaplastic sarcomatous spindle cell component may separate lobules of the malignant chondroid component [24] (**Figure 9** and **Table 10**) [20, 42].

7.6 Differential diagnosis of PEOS

7.6.1 Periosteal chondroma

It is usually smaller and better defined and composed of benign chondroid tissue and does not contain malignant tumor osteoid [24].

7.6.2 Periosteal chondrosarcoma

Radiographically, it contains “popcorn” calcifications, and histologically, it is a low-grade chondrosarcoma containing no tumor osteoid [20, 24].

7.6.3 Parosteal osteosarcoma

Radiographically, this tumor is more radiodense, and histologically this is a low-grade malignant fibro-osseous tumor without chondroid differentiation [20, 24].

7.6.4 Conventional intramedullary osteosarcoma

This is a higher-grade osteosarcoma involving the medullary cavity. Periosteal osteosarcoma does not involve the medullary cavity [24].

Features	PAOS	COS	PEOS	Osteochondroma	Myositis ossificans	Parosteal lipoma
Site and location	Metaphysis	Metaphysis	Metaphysis	Metaphyseal	NOS	NOS
Age in years	10–25	10–25	10–25	10–30	Any age	Any age
Clinical symptoms	Dull pain	Dull pain	Dull pain	No pain	Pain	No pain
Radiology	Radiodense, bosselated, or mushroom-shaped mass arising on the surface of a bone; in long-term lesions, tumor may encircle the bone	Diffuse cortical destruction like Codman's triangle, osteoblastic features	Broad-based surface soft-tissue mass causing extrinsic erosion of thickened underlying diaphyseal cortex and perpendicular periosteal reaction extending into the soft-tissue	Metaphyseal lesions grow in direction opposite to adjacent joint. Cortex and medulla are continuous with underlying bone		Lytic lesions without bony destructions
Histology	Tumor osteoid is arranged in parallel arrays and separated by a hypocellular fibroblastic stroma that exhibits minimal cytologic atypia and minimal mitotic activity without atypical forms	This is a higher-grade osteosarcoma involving the medullary cavity. Periosteal osteosarcoma does not involve the medullary cavity	Osteosarcoma with prominent cartilaginous component. The cartilage in lobules with peripheral spindling and central bone formation. Little no. of mitosis Malignant osteoid/bone is present but may be focal	Bony trabeculae appear normal	Orderly maturation, not attached to underlying bone; more active histologically	Lipocytes, no osteoid

Note: Parosteal Osteosarcoma, PAOS; Conventional Osteosarcoma, COS; Periosteal osteosarcoma, PEOS.

Table 10.
Differential diagnosis of parosteal osteosarcoma, conventional osteosarcoma, periosteal osteosarcoma, osteochondroma, myositis ossificans, and parosteal lipoma.

7.6.5 High-grade surface osteosarcoma

It lacks cartilaginous differentiation. Osteoid component is pleomorphic and high grade [12, 13].

8. High-grade surface osteosarcoma

This is a high-grade osteosarcoma with similar histological features to those of conventional intramedullary osteosarcoma. The tumor grows on the surface and lacks significant medullary involvement. Radiographically it mimics periosteal osteosarcoma, except it has cumulus cloud-like patterns of mineralization. It is a large, lobulated surface mass with variable consistency ranging from soft to firm and may contain hemorrhagic areas. It should not significantly involve the medullary region [13, 24].

8.1 Differential diagnosis of high-grade OS

8.1.1 Dedifferentiated parosteal osteosarcoma

It usually has residual low-grade malignant fibroblastic stromal component. Parosteal osteosarcoma lacks high-grade anaplastic appearance [12, 24].

8.1.2 Conventional intramedullary osteosarcoma

Significant medullary component (minimal medullary component in a high-grade surface osteosarcoma) [24].

8.1.3 Low-grade central osteosarcoma

It is a large, poorly marginated intramedullary mass that either is sclerotic or exhibits trabeculations and histologically similar to parosteal osteosarcoma [12, 24].

9. Summary

Osteosarcoma (OS) is a high-grade malignancy of the bone with high-mortality rate. The exact cause of the condition is unknown, and presently, it is not possible to prevent an osteosarcoma occurrence. It is mainly divided into two types, primary and secondary, based on etiology, while based on where they occur, osteosarcoma is classified as medullary osteosarcoma (occurring in the bone cavity) and surface osteosarcoma (occurring on the bone surface). OS has a bimodal age distribution, having the first peak during adolescence and the second peak in older adulthood, while a little bit more common in males. Some genetic mutations, like mutation of RB and P53 genes, are associated with osteosarcoma. Radiation affected persons, patients of Paget's disease of the bone, fibrous dysplasia, osteoblastoma, Ollier disease, and chemotherapy, are other conditions and disorders that are thought to be associated with Osteosarcomas. The tumor grows slowly in the initial phase of the tumors and may be asymptomatic. Then tumors grow at a moderate rate, and then they suddenly start to rapidly progress. Pathological fractures are commonly seen in long bones.

Three parameters are used for its diagnosis, physical examination with medical history, radiological support (X-rays, CT, MRI), and biopsy for microscopic

examination. To approach the remedy of patient, grading and staging with good differential diagnosis are very important to save the life of the patient.

Conflict of interest

None.

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